British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12822

Treatment of sulfonylurea and insulin overdose

Wendy Klein-Schwartz,[1] Gina L. Stassinos[1] & Geoffrey K. Isbister[2]

[1]Maryland Poison Center, Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, USA and [2]Clinical Toxicology Research Group, University of Newcastle, Newcastle, Australia

Correspondence
Professor Wendy Klein-Schwartz, Pharm. D., MPH, Maryland Poison Center, 220 Arch Street, Room 01-108, Baltimore, MD 21201, USA.
Tel.: +1 (41) 0563 5581
Fax: +1 (41) 0706 7184
E-mail: wkleinsc@rx.umaryland.edu

Keywords
insulin, overdose, sulfonylurea, toxicity

Received
1 June 2015

Accepted
3 November 2015

Accepted Article Published Online
9 November 2015

The most common toxicity associated with sulfonylureas and insulin is hypoglycaemia. The article reviews existing evidence to better guide hypoglycaemia management. Sulfonylureas and insulin have narrow therapeutic indices. Small doses can cause hypoglycaemia, which may be delayed and persistent. All children and adults with intentional overdoses need to be referred for medical assessment and treatment. Unintentional supratherapeutic ingestions can be initially managed at home but if symptomatic or if there is persistent hypoglycaemia require medical referral. Patients often require intensive care and prolonged observation periods. Blood glucose concentrations should be assessed frequently. Asymptomatic children with unintentional sulfonylurea ingestions should be observed for 12 h, except if this would lead to discharge at night when they should be kept until the morning. Prophylactic intravenous dextrose is not recommended. The goal of therapy is to restore and maintain euglycaemia for the duration of the drug's toxic effect. Enteral feeding is recommended in patients who are alert and able to tolerate oral intake. Once insulin or sulfonylurea-induced hypoglycaemia has developed, it should be initially treated with an intravenous dextrose bolus. Following this the mainstay of therapy for insulin-induced hypoglycaemia is intravenous dextrose infusion to maintain the blood glucose concentration between 5.5 and 11 mmol l^{-1}. After sulfonylurea-induced hypoglycaemia is initially corrected with intravenous dextrose, the main treatment is octreotide which is administered to prevent insulin secretion and maintain euglycaemia. The observation period varies depending on drug, product formulation and dose. A general guideline is to observe for 12 h after discontinuation of intravenous dextrose and, if applicable, octreotide.

Introduction

The most common adverse event associated with sulfonylureas and insulin is hypoglycaemia. Insulin and sulfonylureas have narrow therapeutic indices. In diabetics, the overall prevalence of hypoglycaemia is higher with patients treated with insulin (7.3%) than with those treated with oral sulfonylureas (0.8%) [1]. In adults aged 65 years and older, insulin and oral hypoglycaemics are amongst the four most commonly implicated medications leading to emergency hospitalizations, accounting for 13.9% and 10.7% of hospitalizations, respectively [2]. It is therefore not surprising that intentional overdose and unintentional ingestions (e.g. paediatric, therapeutic errors) can cause severe and life-threatening toxicity, which may be delayed and persistent. This paper reviews existing evidence regarding sulfonylurea and insulin toxicity to better guide management of insulin and sulfonylurea overdose.

Epidemiology

In 2013 there were 3950 sulfonylurea and 6967 insulin exposures reported to the US National Poison Data System (NPDS), of which 1590 (40.2%) and 6005 (86.2%), respectively, were single substance exposures [3]. Adults accounted for 45.2% of sulfonylurea and 85.3% of insulin exposures. There were no sulfonylurea deaths and four insulin deaths.

Most sulfonylurea and insulin cases reported to poison centres are unintentional (84.3% and 89.3%, respectively) due to exploratory sulfonylurea ingestions in children and therapeutic errors in adults [3]. Approximately 10% of cases reported to poison centres are intentional (i.e. suicidal, abuse or unknown) [3]. Risk factors for self-harm include a history of diabetes, comorbid psychiatric disorders or, for insulin, employment in a health field where it is accessible [4, 5]. Other less common reasons include criminal intent/malicious or self-administration for secondary gain resulting in factitious hypoglycaemia [6, 7].

Clinical effects of hypoglycaemia

Hypoglycaemia can be severe and prolonged, resulting in neurologic sequelae and death. Signs and symptoms of neuroglycopenia include dizziness, weakness, headache, confusion, drowsiness, coma and seizures [8]. Autonomic symptoms include trembling, palpitations, diaphoresis and nausea. Hypoglycaemia-related dysrhythmias and acute coronary syndrome have been documented and are associated with electrolyte abnormalities, increased release of catecholamines and co-morbid conditions [4, 8, 9]. Electrolyte abnormalities include hypokalaemia and hypomagnesaemia. Insulin overdoses may also present with one or more visible injection sites.

Diabetics may present with symptoms at normal blood glucose if patients tend towards a high baseline, yet longstanding diabetics may have fewer symptoms due to weakened counter-regulatory response [10, 11]. Diabetics with insulin insensitivity may have less glucose utilization for a given dose compared with non-diabetics. In a case series of patients with intentional insulin overdoses, non-diabetics were over three times more likely (P = 0.032) than diabetics to present with serum glucose $<$2.8 mmol l^{-1} (50 mg dl^{-1}) and approximately four times more likely (P = 0.035) to develop recurrent hypoglycaemia during treatment [5].

Pharmacology and toxicology

Sulfonylureas (supplementary Tables 1A and 2A)

Sulfonylureas are insulin secretagogues that modulate the intracellular potential of pancreatic beta islet cells to stimulate calcium mediated insulin release (Figure 1). Sulfonylureas are well absorbed orally, highly plasma protein bound and many have active metabolites [12]. With therapeutic doses, onset of action is usually within 30 min with peak insulinotropic response within 2–3 h. Durations of action are often longer than half-lives.

Sulfonylureas have a narrow therapeutic index and small doses in children and adults can cause hypoglycaemia. Hypoglycaemia has been reported in young children with ingestion of one tablet, including 250 mg chlorpropamide, 5 mg glipizide and 2.5 mg glyburide [13]. In adults, hypoglycaemia can occur with therapeutic use or prescribing errors, so it is not surprising that severe hypoglycaemia occurs with intentional overdoses in both non-diabetic and diabetic patients. Hypoglycaemia may be recurrent and persist for up to 8 days [14–18]. Serious medical outcomes are also more common in deliberate self-poisoning or malicious cases which are attributed to the higher doses [18].

Observation periods for both paediatric and adult poisoning are problematic. The onset of hypoglycaemia in children is usually within 8 h for most patients, but

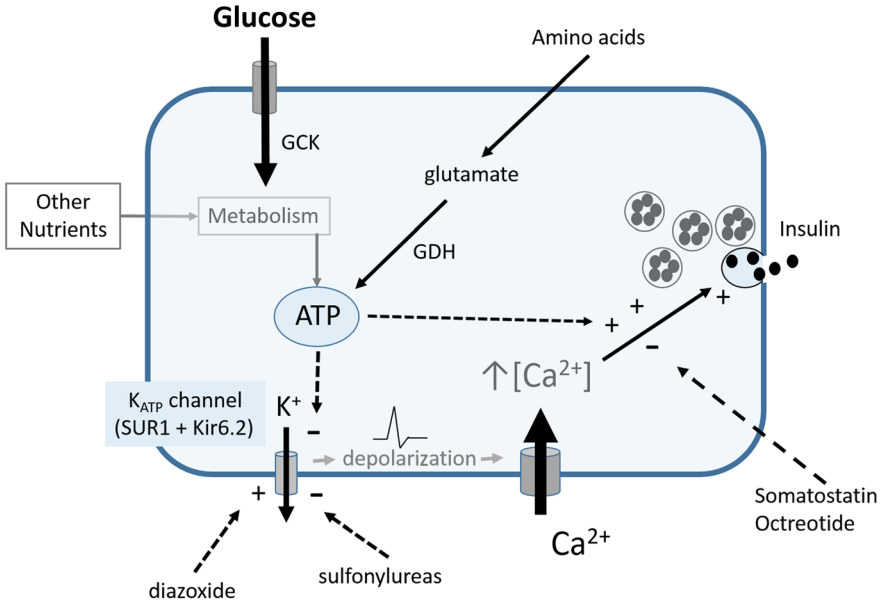

Figure 1

Schematic representation of the pathways involved in the stimulation of insulin secretion. Triggering of insulin secretion occurs from the diffusion of glucose into beta cells, its metabolism to ATP (increased ATP : ADP ratio) which causes the closure of the K_{ATP} channels, membrane depolarization opening voltage operated Ca^{2+} channels, influx of calcium and increased intracellular Ca^{2+} causing exocytosis of vesicles containing insulin. Sulfonylureas stimulate closure of the K_{ATP} channels, diazoxide the opposite. Octreotide decreases cytoplasmic Ca^{2+}. Key: + stimulation; – inhibition; GCK glucokinase; GDH glutamate dehydrogenase; ATP adenosine triphosphate; K_{ATP} channels consist of the SUR1 (sulfonylurea receptor 1) and Kir6.2 (inwardly rectifying potassium channel 6.2)

delayed onset (11–45 h) and recurrence up to 30–70 h have been reported [13, 19–23]. The onset of hypoglycaemia in adult overdoses is usually rapid [15–18]. These findings support medical management in a health care facility for all paediatric sulfonylurea ingestions and adult deliberate self-poisonings. It would be reasonable to observe asymptomatic patients for 12 h and only send them home in daylight, remembering that delayed onset has been reported and patients and parents should be warned of this.

Insulin (supplementary Tables 1B and 2B)

Insulin lowers blood glucose by acting on receptors throughout the body to stimulate glucose uptake and inhibit hepatic glucose production (Figure 1). Insulin is available in ultra-rapid, rapid, intermediate, long acting and combination formulations. Absorption from subcutaneous tissue is an important determinant of onset and duration of action. It may be altered considerably by injection site characteristics [24]. Large single injections can lead to prolonged absorption because of the depot. In contrast, multiple smaller injections will have more rapid absorption. The onset of hypoglycaemia can be as soon as 1–2 h or be delayed over 18 h after insulin glargine overdose [25, 26]. Duration of action may be prolonged a few days to a week after an overdose and larger doses have been associated with longer duration, but not the type of insulin [4, 10, 27–30]. This may be due to changed absorption profiles of even short-acting insulin due to large injection depots. Insulin's oral bioavailability is less than 1%, so rarely massive ingestions may lead to hypoglycaemia [31].

Severe and prolonged hypoglycaemia occurs in adult deliberate self-poisoning and malicious overdoses, with reported blood glucose nadirs below 1.7 mmol l^{-1} (30 mg dl^{-1}). There is a poor relationship between insulin dose and severity or outcomes [4, 5, 10, 27, 32, 33], with deaths occurring after 400 units and no effects after 3300 units [25, 34]. Other factors associated with poor outcomes include co-ingestants and patient comorbidities [4, 35].

Risk assessment and observation recommendations

All children and non-diabetics who unintentionally ingest a sulfonylurea, all intentional ingestions of sulfonylureas and all intentional injections of insulin should be managed in a health care facility (Figure 2). Several poison centre studies have concluded that adults with therapeutic errors can be safely monitored and treated with carbohydrate supplementation at home [32, 33, 36]. Those who become clinically symptomatic, experience persistent hypoglycaemia or lack the ability to monitor blood glucose need emergency referral to a health care facility.

A range of observation periods from 8 to 24 h have been recommended for unintentional sulfonylurea ingestions in children [13, 19–22, 37–39] due to the complexities associated with developing hypoglycaemia, including whether the child is fasted, given food or intravenous prophylactic glucose. Lung *et al.* showed that the onset may be >8 h in children freely given food or intravenous dextrose, but this was within 15 h (excluding one discharged patient returning at 18 h) [19]. Delayed onset of hypoglycaemia almost always occurred when the child was sleeping. Therefore a safe recommendation is to monitor all children for 12 h, except if this would lead to discharge during the night when they should be kept until the following morning. Children should be allowed food as fasting for >3 h is impractical. Intravenous glucose is not required, because it provides only a small amount of glucose (e.g. 10 g h^{-1} for 10% dextrose at 100 ml h^{-1}) [39]. Observation periods for adult intentional ingestions of sulfonylureas are less problematic because hypoglycaemia should develop within 6–12 h, irrespective of the administration of dextrose, either oral or intravenous. Similarly the onset of hypoglycaemia following deliberate administration of insulin in adults is usually rapid (within hours), but longer onsets have been reported [4, 25, 26]. The observation period for asymptomatic patients with an intentionally administered large quantity of insulin, especially long acting, is at least 18 h [25].

For sulfonylureas and insulin, persistent hypoglycaemia may last for days and patients should be observed for sufficient time after discontinuing supplemental dextrose. This time period will vary depending on the pharmacodynamic/pharmacokinetic profile of the sulfonylurea or insulin formulation involved and the dose.

Non-diabetics and diabetics with pancreatic function treated with intravenous dextrose should be monitored for recurrence of hypoglycaemia after dextrose is ceased. A general guideline is an observation period of 12 h after intravenous dextrose and, if applicable, octreotide are discontinued. Delayed recurrence of hypoglycaemia has been reported and those with overdoses of long acting insulin may require longer observation times. Close observation is particularly relevant when excessive dextrose has caused transient hyperglycaemia (>10 mmol l^{-1}), as this stimulates endogenous insulin release with resultant much higher risk of rebound hypoglycaemia.

Laboratory monitoring

Hypoglycaemia is usually defined as a blood glucose concentration less than 3.3 mmol l^{-1} (60 mg dl^{-1}). In the context of sulfonylurea or insulin exposure, higher blood glucose concentrations with autonomic or neuroglycopenic symptoms are also considered hypoglycaemia. It is generally recommended that blood

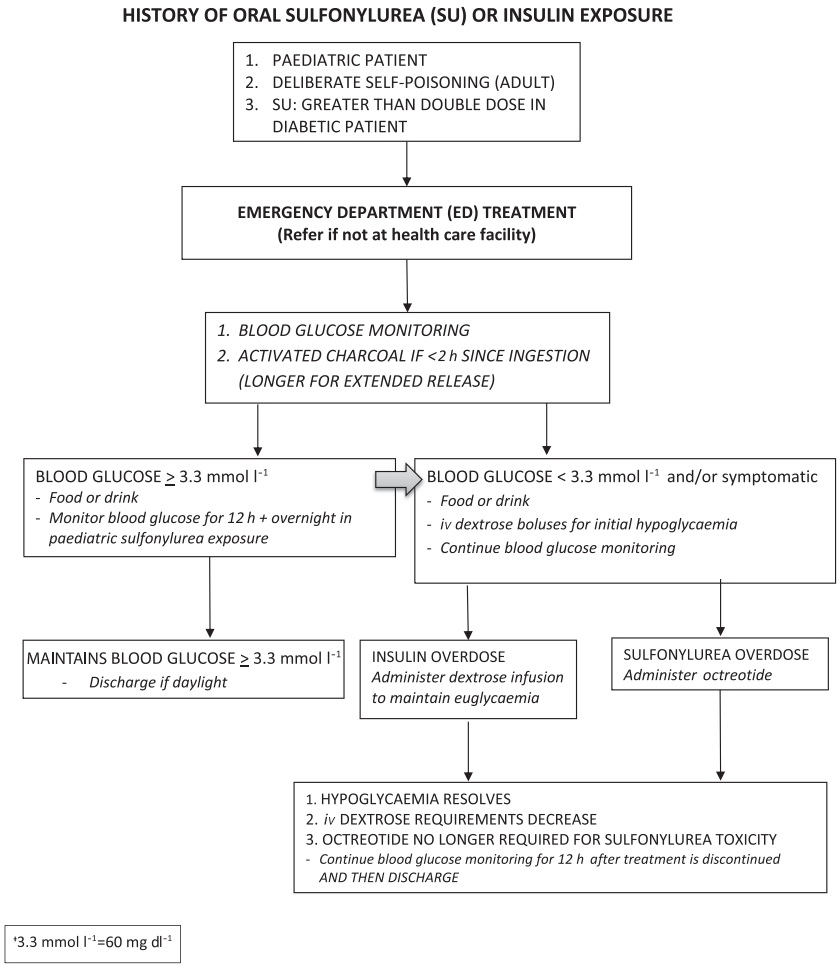

Figure 2
Algorithm for management of sulfonylurea and insulin exposures

glucose be monitored hourly initially and then at longer intervals (2–6 h) in a hospital setting. A different approach has been suggested for asymptomatic children with sulfonylurea ingestions to avoid frequent painful blood glucose testing [40]. In awake and alert asymptomatic children, initial 3–6 h post-ingestion blood glucose should be obtained and then every 2–3 h while asleep. Children with symptoms should have immediate blood glucose and those with borderline blood glucose should have it repeated in 1 h.

Although sulfonylureas may be detected in blood or urine, this test is usually not available. Laboratory evaluation of C peptide level and its ratio to serum insulin can be useful if the presence of exogenous insulin is in question. Endogenous insulin originates as a conjugate with C peptide. The C peptide : insulin ratio is greater than 1 and they are both elevated. With exogenous insulin, the ratio of C peptide : insulin is less than 1. The triad of simultaneous hypoglycaemia, high insulin levels and suppressed C peptide is generally recognized as pathognomonic for exogenous insulin administration [41]. Electrolytes including potassium, magnesium and phosphate should be monitored.

Treatment

Supplementary Tables 2A and 2B describe findings from studies that address toxicity and treatment of sulfonylurea and insulin-induced hypoglycaemia. The tables focus on the following interventions: enteral supplementation, intravenous dextrose and octreotide. Table 1 summarizes recommended treatments.

GI decontamination

Activated charcoal should be given within 2 h of ingestion of immediate release sulfonylureas and can be considered beyond this for extended release products [42].

Table 1

Recommended treatments for hypoglycaemia from sulfonylurea and insulin

Treatment	Hypoglycaemia* related indication	Route	Adult dose	Paediatric dose	Adverse effects
Dextrose (25–50%) (D25W or D50W)	Initial control	i.v.	50–100 ml of 50% (25–50 g)	2–4 ml kg^{-1} of 25% (0.5–1 g kg^{-1})	Hyperglycaemia, phlebitis and cellulitis if injection site extravasation, serum hyperosmolality
Dextrose (5–20%)	Persistent hypoglycaemia	i.v. infusion	Titrate prn	Titrate prn	Hyperglycaemia
Octreotide	Recurrent hypoglycaemia (sulfonylureas)	s.c. (preferred), i.v.	50–100 μg every 6–12 h prn	1–2 μg kg^{-1} every 6–12 h prn	Hyperglycaemia, nausea, abdominal pain, diarrhoea, bradycardia
Glucagon	i.v. access not available	i.m., i.v., s.c.	1 mg, may repeat	0.5–1 mg or 0.02–0.03 mg kg^{-1}, may repeat	Hyperglycaemia, hypokalaemia

*Blood glucose concentration < 3.3 mmol l^{-1} (60 mg dl^{-1}) or autonomic or glycopenic symptoms (see text). i.v. = intravenous; s.c. = subcutaneous; i.m. = intramuscular; prn = as needed

Enteral supplementation

Free access to food is recommended in patients who are alert and able to tolerate oral intake. In patients who are initially hypoglycaemic with altered mental status, intravenous dextrose should be administered for initial control. Once hypoglycaemia is corrected, the patient should be fed complex carbohydrates.

Dextrose

Although intravenous dextrose would seem the obvious therapy for hypoglycaemia, excessive dextrose will cause hyperglycaemia and a marked increase in endogenous insulin secretion in patients with an intact pancreas, including both non-diabetics and type II (insulin-resistant) diabetics [43]. This is more problematic with sulfonylurea toxicity where small increases in blood glucose may greatly stimulate insulin release even within the normoglycaemic range. The other major problem with intravenous dextrose is that it only provides a small amount of glucose unless 50% dextrose is used, for example 100 ml h^{-1} of 10% dextrose only provides 10 g h^{-1}.

Despite these caveats, in both insulin and sulfonylurea overdoses, the initial management of hypoglycaemia is a 0.5 to 1 g kg^{-1} bolus of intravenous dextrose, D50W (50% dextrose) in adults and D25W (25% dextrose) or D10W (10% dextrose) in children [8, 44]. Following this in insulin overdoses patients should receive a 10 to 50% dextrose infusion with the concentration and rate titrated to maintain euglycaemia (5.5 to 11 mmol l^{-1}) [5]. Exact dextrose requirements are difficult to predict. Significant correlations have been found between insulin dose and duration of dextrose infusion [4, 5, 10, 27, 45], but not total intravenous dextrose amount required [4, 5, 27]. In 25 patients with overdoses of rapid to long-acting insulin, dextrose doses varied widely (184 to 1056 g). The average maximum infusion rate was 29.5 g h^{-1} (17.5–41.1) [27]. In insulin overdoses, overall dextrose requirements may be similar in non-diabetics and diabetics [5]. Some studies report success using plasma insulin levels to guide dextrose infusion adjustments [46–48].

In insulin dependent diabetic patients, as toxicity from the overdose diminishes there is usually a sharp rise in the blood glucose concentrations and consideration should be given as to the appropriate time to reinstitute anti-hyperglycaemic drug therapy. In non-diabetics it can be far more difficult to determine when there is no further exogenous insulin present, because the administration of intravenous dextrose will cause endogenous insulin production, preventing a rise in the blood sugar concentration [27]. Measurement of C-peptide concentrations may assist in determining this because they will rise as the exogenous insulin is cleared [41]. Although not reported, theoretically the administration of octreotide could also diagnose that endogenous insulin is responsible for ongoing hypoglycaemia. This would lead to a rapid rise in blood glucose concentrations in the absence of exogenous insulin.

Following an initial bolus of intravenous dextrose in a sulfonylurea overdose, excessive intravenous dextrose will stimulate endogenous insulin production (most patients will have intact pancreatic function). This contributes to subsequent hypoglycaemia, and potentially further boluses of dextrose, leading to a vicious cycle of repeated dextrose boluses and rebound hypoglycaemic episodes. For this reason octreotide, rather than intravenous dextrose, should be the main treatment in sulfonylurea overdoses.

Potential adverse effects of intravenous dextrose include hyperglycaemia, phlebitis (worse with higher concentrations of dextrose) and cerebral toxicity associated with hyperosmolar syndrome, especially in children [49].

The use of prophylactic intravenous dextrose (i.e. prior to the first development of hypoglycaemia) is problematic. Delayed hypoglycaemia is well reported after prophylactic intravenous dextrose for sulfonylureas [13, 22, 37, 50]. Although the extent to which prophylactic intravenous dextrose contributes to delayed hypoglycaemia is unclear, it is not recommended. When intravenous dextrose is discontinued, hypoglycaemia

may occur in patients still unable to maintain normal blood glucose [39].

While insulin or sulfonylurea dose, formulation and plasma insulin level, if available, can help frame the management plan for dextrose administration (e.g. magnitude of dextrose requirement and anticipated duration of therapy), they do not replace frequent blood glucose monitoring as the basis for treatment decisions.

Octreotide

Octreotide is a long-acting synthetic somatostatin analogue that binds to somatostatin-2 receptors on the pancreatic beta cells, preventing the influx of calcium required for insulin secretion and therefore blocks insulin secretion. It has been used in the treatment of hypoglycaemia resulting from sulfonylurea toxicity for over 20 years [15], and safely for numerous other conditions prior to this. It is safe and only causes minor adverse effects, including injection site pain, hyperglycaemia, nausea, abdominal pain, flatulence, diarrhoea and bradycardia.

In most reported cases, octreotide has been used after recurrent hypoglycaemia following intravenous dextrose [15, 16, 51]. Dextrose stimulates insulin release causing hypoglycaemia. This cycle is perpetuated with re-administration of intravenous dextrose. Although many recommend octreotide in patients with sulfonylurea overdoses who experience rebound hypoglycaemia, it makes more sense for it to be commenced after the first episode of hypoglycaemia. There are no controlled trials, so dose and dosing interval are based on limited published data. The dose can be given intravenously (50 μg bolus followed by an infusion of 25 μg h^{-1}, 1 μg kg^{-1} h^{-1} in children) or subcutaneously (50–100 μg in adults and 1–2 μg kg^{-1} in children every 6–12 h [16, 40, 52, 53] Octreotide should be initially given for 12 h.

In 13 published cases of octreotide use for sulfonylurea toxicity, the average number of pre- and post-octreotide hypoglycaemic episodes, respectively, was 3.3 and 0.4 [51]. Patients with acute overdoses treated earlier received three to four doses of octreotide compared with one to two doses in patients presenting after 8 h. This may reflect lower risk of hypoglycaemia with time due to drug metabolism. Hypoglycaemic episodes post-octreotide occurred more frequently in patients with chronic toxicity from therapeutic use (42.4%) than acute overdoses (30%). An animal study found that octreotide doses of 50–100 μg decreased the number of hypoglycaemic episodes by a quarter [54]. An observational study in children [23] and two case series in adults [15, 16] reported fewer hypoglycaemic episodes with octreotide. The reports in adults also noted lower dextrose requirements (Supplementary Table 2A).

In a placebo controlled trial of adults with hypoglycaemia who were on a sulfonylurea alone or in combination with another anti-hyperglycaemic drug or insulin, 18 received standard treatment [one ampoule D50W (50% dextrose) intravenously and oral carbohydrates] and placebo (1 ml normal saline subcutaneously) while 22 received standard treatment plus 75 μg of octreotide subcutaneously [55]. The mean blood glucose concentrations were significantly higher in the octreotide patients from 4 to 8 h after octreotide but not in subsequent hours. Limitations include the fact that patients on insulin were included and oral caloric intake varied. This trial did not include deliberate large overdoses, so findings may not be generalizable. A three arm crossover study was performed in eight normal subjects [56]. All subjects received 1.43 mg kg^{-1} glipizide and 50% dextrose followed by either dextrose infusion or octreotide (30 ng kg^{-1} min^{-1}) or diazoxide (300 mg intravenously every 4 h with dextrose). All drugs were stopped at 13 h. Dextrose requirements for the dextrose only and diazoxide groups were similar and significantly higher than dextrose requirements for the octreotide arm. Plasma insulin concentrations were approximately five times lower with octreotide. After treatment was stopped hypoglycaemia recurred in all subjects with intravenous dextrose and diazoxide but in only two subjects in the octreotide arm.

Glucagon

Glucagon increases blood glucose by promoting glycogenolysis and gluconeogenesis. It can be given intramuscularly so it has a role when intravenous dextrose is not an option such as in the pre-hospital setting or when intravenous access is unavailable. Onset is within 5–20 min and duration of action is under 1 h. Adverse effects include nausea and vomiting [6]. Glucagon should not be routinely administered as it induces insulin release and is not useful in patients with glycogen depletion.

Management of sequelae

In addition to supplemental dextrose, appropriate management of electrolyte disturbances is important. In some cases oral or intravenous potassium repletion may be necessary. However, because hypokalaemia is due to intracellular potassium shift, over-aggressive repletion of potassium should be avoided.

Patients who present with severe depressed mental status and do not initially respond to intravenous dextrose boluses may require intubation and ventilation. Adult respiratory distress syndrome and pulmonary oedema may also contribute to respiratory distress. Supplemental dextrose is the initial treatment of

hypoglycaemia-induced seizures, with benzodiazepines used as adjunct therapy.

Conclusions

When managing patients with sulfonylurea and insulin toxicity, monitoring and triage decisions must consider the possibility of delayed and persistent hypoglycaemia. Although the level of evidence is low, the data support the following recommendations:

(1) Prophylactic intravenous dextrose is not recommended. Alert patients should be fed.
(2) Blood glucose concentration should be assessed frequently.
(3) Initial treatment of hypoglycaemia is an intravenous dextrose bolus. In insulin overdoses treatment should be continued with food and/or intravenous dextrose to maintain euglycaemia.
(4) In sulfonylurea exposure (children) or overdose (adults) octreotide should be administered after the initial correction of hypoglycaemia with intravenous dextrose.
(5) Patients treated with intravenous dextrose and/or octreotide should not be discharged until sufficient time has elapsed post-discontinuation of therapy to exclude recurrent hypoglycaemia. This time period varies but a general guideline is an observation period of 12 h after intravenous dextrose and, if applicable, octreotide are discontinued. Patients should never be discharged late at night.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 Unger J. Uncovering undetected hypoglycemic events. Diabetes Metab Syndr Obes 2012; 5: 57–74.

2 Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older adults. N Engl J Med 2011; 365: 2002–12.

3 Mowry JB, Spyker DA, Cantilena LR, McMillan N, Ford M. 2013 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st annual report. Clin Toxicol 2014; 52: 1032–283.

4 Arem R, Zoghbi W. Insulin overdose in eight patients: insulin pharmacokinetics and review of the literature. Medicine (Baltimore) 1985; 64: 323–32.

5 Stapczynski JS, Haskell RJ. Duration of hypoglycemia and need for intravenous glucose following intentional overdoses of insulin. Ann Emerg Med 1984; 13: 505–11.

6 Wong OF, Tsui KL, Kam CK. A case of acute insulin poisoning. Hong Kong J Emerg Med 2006; 13: 232–4.

7 Glatstein M, Garcia-Bournissen F, Scolnik D, Koren G, Finkelstein Y. Hypoglycemia in a healthy toddler. Ther Drug Monit 2009; 31: 173–7.

8 Clayton D, Woo V, Yale JF. Hypoglycemia. Can J Diabetes 2013; 37: S69–71.

9 Kamijo Y, Soma K, Aoyama N, Fukuda M, Ohwada T. Myocardial infarction with acute insulin poisoning– a case report. Angiology 2000; 51: 689–93.

10 Samuels MH, Eckel RH. Massive insulin overdose: detailed studies of free insulin levels and glucose requirements. J Toxicol Clin Toxicol 1989; 27: 157–68.

11 Skolnik AB, Ewald MB. Case files of the Harvard Medical Toxicology Fellowship at Children's Hospital Boston: an insulin overdose. J Med Toxicol 2010; 6: 413–9.

12 Ferner RE, Chaplin S. The relationship between the pharmacokinetics and pharmacodynamics effects of oral hypoglycaemic drugs. Clin Pharmacokinet 1987; 12: 379–401.

13 Quadrani DA, Spiller HA, Widder P. Five year retrospective evaluation of sulfonylurea ingestion in children. J Toxicol Clin Toxicol 1996; 34: 267–70.

14 Palatnik W, Meatherall RC, Tenenbein M. Clinical spectrum of sulfonylurea overdose and experience with diazoxide. Arch Intern Med 1991; 151: 1859–62.

15 Carr Zed PJ. Octreotide for sulfonylurea-induced hypoglycemia following overdose. Ann Pharmacother 2002; 36: 1727–32.

16 McLaughlin SA, Crandall CS, McKinney PE. Octreotide: an antidote for sulfonylurea-induced hypoglycemia. Ann Emerg Med 2000; 36: 133–8.

17 Rambo C, Queralt Y. Prolonged hypoglycemia following acute glimiperide overdose. J Toxicol Clin Toxicol 1998; 36: 437.

18 Forrester MB. Adult glyburide ingestions reported to Texas poison control centers, 1998 2005. Hum Exp Toxicol 2007; 26: 563–71.

19 Lung DD, Olson KR. Hypoglycemia in pediatric sulfonylurea poisoning: an 8-year poison center retrospective study. Pediatrics 2011; 127: e1558–64.

20 Glatstein M, Garcia-Bournissen F, Scolnik D, Koren G. Sulfonylurea intoxication at a tertiary care paediatric hospital. Can J Clin Pharmacol 2010; 17: e51–6.

21 Levine M, Ruha A, LoVecchio F, Riley BD, Pizon AF, Burns BD, Thomas SH. Hypoglycemia after accidental pediatric sulfonylurea ingestions. Pediatr Emerg Care 2011; 27: 846–9.

22 Spiller HA, Villalobos D, Krenzelok EP, Anderson BD, Gorman SE, Rose SR, Fenn J, Anderson DL, Muir SJ, Rodgers GC Jr Prospective multicenter study of sulfonylurea ingestion in children. J Pediatr 1997; 131: 141–6.

23 Dougherty PP, Lee SC, Lung D, Klein-Schwartz W. Evaluation of the use and safety of octreotide as antidotal therapy for sulfonylurea overdose in children. Pediatr Emerg Care 2013; 29: 292–5.

24 Mudaliar S, Mohideen P, Deutsch R, Ciaraldi TP, Armstrong D, Kim B, Sha X, Henry RR. Intravenous glargine and regular insulin have similar effects on endogenous glucose output and peripheral activation/deactivation kinetic profiles. Diabetes Care 2002; 25: 1597–602.

25 Munck O, Quaade F. Suicide attempted with insulin. Dan Med Bull 1963; 10: 139.

26 Kumar A, Hayes CE, Iwashyna SJ, Boustani R, Duncan L, Mickell JJ, Francis G. Management of intentional overdose of insulin glargine. Endocrinol Nutr 2012; 59: 570–2.

27 Megarbane B, Deye N, Bloch V, Sonneville R, Collet C, Launay M, Baud F. Intentional overdose with insulin: prognostic factors and toxicokinetic/toxicodynamic profiles. Crit Care 2007; 11: R115.

28 Shibutani Y, Ogawa C. Suicidal insulin overdose in a type 1 diabetic patient: relation of serum insulin concentrations to the duration of hypoglycemia. J Diabetes Complications 2000; 14: 60–2.

29 Hale PJ, Fitzgerald MG, Wright AD, Nattrass M. Attempted suicide by insulin administration. Pract Diab Int 1985; 2: 42–4.

30 Ohyama T, Saisho Y, Muraki A, Kawai T, Itoh H. Prediction of recovery time from hypoglycemia in patients with insulin overdose. Endocr J 2011; 58: 607–11.

31 Svingos RS, Fernandez EM, Reeder DN, Parker JJ. Life-threatening hypoglycemia associated with intentional insulin ingestion. Pharmacotherapy 2013; 33: e28–33.

32 Glogan D, Levitan RD, Brooks DE, Gerkin RD. Unintentional use of mistaken insulin products: a retrospective review of poison center data. J Emerg Med 2013; 45: 547–53.

33 Beuhler MC, Spiller HA, Aleguas A. Demographics and outcome of unintentional insulin overdoses managed by three poison centers. Clin Toxicol (Phila) 2013; 51: 789–93.

34 Groth CM, Banzon ER. Octreotide for the treatment of hypoglycemia after insulin glargine overdose. J Emerg Med 2013; 45: 194–8.

35 Martin FI, Hansen N, Warne GL. Attempted suicide by insulin overdose in insulin requiring diabetics. Med J Aust 1977; 1: 58–60.

36 Cantrell FL, Clark RF. Supratherapeutic dose of sulfonylureas in diabetic patients: how much is too much? Clin Toxicol 2007; 45: 482–4.

37 Borowski H, Caraccio T, Mofenson H. Sulfonylurea ingestion in children: is an 8-h observation period sufficient? J Pediatr 1998; 133: 584–5.

38 Burkhart KK. When dose hypoglycemia develop after sulfonylurea ingestion? Ann Emerg Med 1998; 31: 771–2.

39 Kokan L, Dart RC. Oral hypoglycemics: ACMTnet concurs. Clin Toxicol 1996; 34: 271–2.

40 Calello DP, Kelly A, Osterhoudt KC. Case files of the medical toxicology fellowship program at the children's hospital of Philadelphia: a pediatric exploratory sulfonylurea ingestion. J Med Toxicol 2006; 2: 19–24.

41 Scarlett JA, Mako ME, Rubenstein AH, Blix PM, Goldman J, Horwitz DL, Tager H, Jaspan JB, Stjernholm MR, Olefsky JM. Factitious hypoglycemia. Diagnosis is by measurement of serum C-peptide immunoreactivity and insulin-binding antibodies. N Engl J Med 1977; 297: 1029–32.

42 Kivistö KT, Neuvonen PJ. The effect of cholestyramine and activated charcoal on glipizide absorption. Br J Clin Pharmacol 1990; 30: 733–6.

43 Henquin JC. Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes 2000; 49: 1751–60.

44 Wherrett D, Huot C, Mitchell B, Pacaud D. Type 1 diabetes in children and adolescents. Can J Diabetes 2013; 37 (Suppl 1): S153–62.

45 Page MM, Alberti KG, Greenwood R, Gumaa KA, Hockaday TD, Lowy C, Nabarro JD, Pyke DA, Sönksen PH, Watkins PJ, West TE. Treatment of diabetic coma with continuous low-dose infusion of insulin. Br Med J 1974; 2: 687–90.

46 DeFronzo RA, Ferrannini E, Hendler R, Felig P, Wahren J. Regulation of splanchnic and peripheral glucose uptake by insulin and hyperglycemia in man. Diabetes 1983; 32: 35–45.

47 Lee P, Greenfield JR, Center JR, Campbell LV. Plasma insulin concentration is useful to guide glucose supplement in insulin overdose. Intensive Care Med 2009; 35: 181–2.

48 Mork TA, Killeen CT, Patel NK, Dohnal JM, Karydes HC, Leikin JB. Massive insulin overdose managed by monitoring daily insulin levels. Am J Ther 2011; 18: e162–6.

49 Shah A, Stanhope R, Matthew D. Hazards of pharmacological tests of growth hormone secretion in childhood. BMJ 1992; 304: 173–4.

50 Szlatenyi CS, Capes KF, Wang RY. Delayed hypoglycemia in a child after ingestion of a single glipizide tablet. Ann Emerg Med 1998; 31: 773–6.

51 Dougherty PP, Klein-Schwartz W. Octreotide's role in the management of sulfonylurea-induced hypoglycemia. J Med Toxicol 2010; 6: 199–206.

52 Toxicology and Wilderness Medicine, 2nd edition. Melbourne: Therapeutic Guidelines; 2012: 142–145.

53 Llamado R, Czaja A, Stence N, Davidson J. Continuous octreotide infusion for sulfonylurea-induced hypoglycemia in a toddler. J Emerg Med 2013; 45: e209–13.

54 Gul M, Cander B, Girisgin S, Ayan M, Kocak S, Unlu A. The effectiveness of various doses of octreotide for sulfonylurea-induced hypoglycemia after overdose. Adv Ther 2006; 23: 878–84.

55 Fasano CJ, O'Malley G, Dominici P, Aguilera E, Latta DR. Comparison of octreotide and standard therapy versus standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. Ann Emerg Med 2008; 51: 400–6.

56 Boyle PJ, Justice K, Krentz AJ, Nagy RJ, Scheade DS. Octreotide reverses hyperinsulinemia and prevents hypoglycemia induced by sulfonylurea overdoses. J Clin Endocrinol Metab 1993; 76: 752–6.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table 1A
Sulfonylurea formulations
Table 1B
Insulin formulations
Table 2A
Sulfonylurea studies
Table 2B
Insulin studies